

The European Society of Paediatric Oncology Ependymoma-II Program Core-Plus Model: Development and Initial Implementation of a Cognitive Test Protocol for an International Brain Tumour Trial

S Thomas^{1,2}, D Reynolds^{1,2}, MCHJ Morrall³, J Limond⁴, M Chevignard^{5,6}, G Calaminus⁸, G Poggi⁷, E Bennett¹, D Frappaz¹⁰, D Slade⁹, J Gautier¹⁰, P McQuilton^{1,2}, M Massimino¹¹, R Grundy²

Institutions:

1. Department of Paediatric Neuropsychology, Nottingham Children's Hospital, Queen's Medical Centre, Nottingham, NG7 2UH, UK
2. Child Brain Tumour Research Centre, School of Medicine, University of Nottingham, Queen's Medical Centre, Nottingham, NG7 2UH, UK
3. Department of Paediatric Neuropsychology, Leeds General Infirmary, Leeds LS1 3EX
4. Psychology, College of Life and Environmental Sciences, Washington Singer Laboratories, University of Exeter, Perry Road EX4 4QG
5. Rehabilitation Department for children with acquired neurological injury; Saint Maurice Hospitals, 14, rue du Val d'Osne, 94410, Saint Maurice, France
6. Sorbonne Université, CNRS, INSERM, Laboratoire d'Imagerie Biomédicale, LIB, 75006 Paris
7. Neuro-Oncological Rehabilitation Unit- IRCCS E. Medea - Bosisio Parini –Lecco
8. University Children's Hospital Bonn, Adenauerallee 119, 53113 Bonn, Germany.
9. Cancer Research UK Clinical Trials Unit (CRCTU), Institute of Cancer and Genomic Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT
10. Institut d'Hématologie Oncologie pédiatrique, Lyon, France
11. Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Corresponding author: Dr Sophie Thomas, Consultant Paediatric Neuropsychologist, Department of Paediatric Neuropsychology, Nottingham Children's Hospital, Queen's Medical Centre, Nottingham, NG7 2UH, UK sophie.thomas@nhs.net

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Abstract

It is increasingly accepted that survival alone is an inadequate measure of the success of childhood brain tumour treatments. Consequently, there is increasing emphasis on capturing quality of survival. Ependymomas are the third most frequently occurring brain tumours in childhood and present significant clinical challenges. European Society of Paediatric Oncology Ependymoma II is a comprehensive international program aiming to evaluate outcomes under different treatment regimens and improve diagnostic accuracy. Importantly, there has been agreement to lower the age at which children with posterior fossa ependymoma undergo focal irradiation from three years to either eighteen months or one year of age. Hitherto radiotherapy in Europe had been reserved for children over three years due to concerns over adverse cognitive outcomes following irradiation of the developing brain. There is therefore a duty of care to include longitudinal cognitive follow-up and this has been agreed as an essential trial outcome. Discussions between representatives of 18 participating European countries over 10 years have yielded European consensus for an internationally accepted test battery for follow-up of childhood ependymoma survivors. The 'Core-Plus' model incorporates a two-tier approach to assessment by specifying core tests to establish a minimum dataset where resources are limited, whilst maintaining scope for comprehensive assessment where feasible. The challenges leading to the development of the Core-Plus model are presented alongside learning from the initial stages of the trial. We propose that this model provides a solution for future international trials addressing both childhood brain tumours and other conditions associated with cognitive morbidity.

Keywords

Cognitive, Assessment, Brain Tumour, Late Effects, Radiotherapy, Quality of Survival

1. Introduction

The rise in overall 5-year survival rates for childhood brain tumours to over 72.7% [1] is accompanied by increased discussion surrounding the clinical management of childhood tumours with poorer prognosis such as high risk medulloblastoma, high grade glioma and ependymoma. Amidst these considerations is a growing emphasis on the importance of maximising and measuring quality of survival (QoS) to inform treatment decisions. There are a far greater number of post cancer life-years for childhood versus adult brain tumour survivors and these years are likely to include key educational milestones and academic skills acquisition, alongside the development of social skills, self-efficacy and personal identity, all of which are essential components of wellbeing and quality of survival.

Childhood brain tumour survivors often experience decline in overall intelligence quotient (IQ) and academic attainment [2]. A review of 39 studies also identified negative effects upon verbal and non-verbal IQ, attention, psychomotor skills, visuospatial abilities, verbal memory, language, reading, mathematics and spelling [3]. Many children suffer deficits across multiple domains, which is unsurprising given that cognitive processes overlap and interact during childhood [4] [5]. However, there is considerable variability in outcomes which translates to significant difficulty predicting outcome for individual patients. An integrative analysis incorporating 18 studies and 403 patients found a mean average IQ of 91 but a large standard deviation of 24.1 IQ points [6]. However, a number of treatment, individual and comorbidity factors have been found predictive of more severe impairment. These commonly include age at treatment, tumour location, gender, type of surgery, presence of hydrocephalus, cerebellar mutism, dose of radiation therapy, chemotherapy, seizures and recurrent disease [6]. Of these, radiotherapy has been identified as one of the most crucial risk factors. Reimers et al (2003) reported a mean IQ of 78.8 (SD=14.3) for irradiated childhood brain tumour patients compared with 97.1 (SD=14.3) for non-irradiated patients [7]. Age was found to be a significant factor with younger children less than 4 years old receiving whole brain irradiation

demonstrating a 14-point deficit relative to older counterparts (mean = 73.4 vs. 87.0; $p < 0.05$) [6]. Individual presentation at diagnosis and treatment complications such as posterior fossa syndrome are also likely to greatly influence cognitive and academic outcome alongside socio-economic variables [8].

2. Ependymoma

Ependymoma is the third most frequently occurring central nervous system tumour in children [9] and presents significant clinical management challenges often due to the young age at presentation and close involvement of the brain stem and cerebellum or eloquent areas of the supratentorial region. Despite improvements in overall childhood brain tumour morbidity, ependymoma survival rates have not improved significantly. Patients with completely resected tumours have been found to have an event free survival rate of approximately 78% compared with an event free survival rate of approximately 43% for those with near total or subtotal resection [10]. The extent of surgical resection has for several years been the most significant clinical prognostic marker in ependymoma known to be associated with survival [11].

Increases in survival are often at the expense of the quality of this survival, and there remain differences in international clinical practice. For example, the employment of radiotherapy deferral strategies in children under three years of age in Europe contrasts with the use of conformal radiotherapy in this younger age group in North America [12]. Concerns regarding toxicity of radiotherapy to younger children are fundamental to ependymoma management where over 50% of children are under 5 years old at diagnosis [13] given the potential risks of irradiating the immature brain and the growing knowledge surrounding the potential role of the cerebellum in broader cognitive functions including literacy acquisition [14]. Consequently, there have been efforts to assess the role of primary chemotherapy strategies in avoiding or delaying radiotherapy in children under 5

years of age. The 'Baby Brain' protocol was applied to 88 UK children diagnosed with ependymoma between 1992 and 2004 finding that radiotherapy can be avoided or delayed in a substantial proportion of these children without compromising overall survival [15] or quality of survival [16].

A systematic review of numerous studies reporting cognitive outcomes in ependymoma was also conducted by Morrall et al [12]. Detrimental findings included significant decline in processing speed, visuospatial organisation [17], attention, memory [18] and poorer reading attainment at 5 year follow up [19]. Nine papers included in the review produced a sample of 184 children, 36% of whom were reported to have been irradiated aged 36 months or younger (80% received infratentorial radiotherapy and 14% supratentorial). Evidence of the impact of radiation was inconsistent. Merchant et al reported radiation dosimetry to be the most significant determinant of IQ [20]. One study concluded radiation prior to three years of age to be highly hazardous to cognitive outcomes [21] and another reported smaller learning increments over time in those irradiated at a younger age [22]. Decline in IQ in an irradiated sample was observed more than 4 years post diagnosis [23] and seen to affect reading ability [19]. Conversely, six papers identified by Morrall et al indicated conformal radiotherapy was not associated with poorer cognitive outcome [24] [25] [26] [27] [28] [29]. Merchant et al [10] reported that their young irradiated group had poorer IQ at baseline prior to radiotherapy and that this improved over time, and Poggi et al found pre-/perioperative damage more predictive of cognitive outcome than age at radiotherapy [30]. Supratentorial tumor location and multiple surgeries were predictive of worse baseline pre-radiotherapy reading performance and performance decline was seen to be predicted by gender, longer symptomatic interval, hydrocephalus, additional chemotherapy prior to radiotherapy and pre-existing endocrine deficiencies [19].

Whilst these studies provide indicators of the intellectual functions likely to be vulnerable in children treated with ependymoma, data are too limited for comparison or appropriate statistical interrogation. The review by Morrall et al (2014) [12] revealed variation in reporting of intervention

variables such as radiation dosimetry, and considerable discrepancies in approaches to cognitive testing and its reporting. Thirteen different psychometric measures were employed, three of which were proxy questionnaire measures. Three studies reported ability or attainment findings without specifying their measures. Overall, there is contradictory evidence in the literature so far with respect to the significance of radiotherapy toxicity, the risks and benefits of differing radiotherapy regimes, and a requirement to investigate outcomes of newer radiotherapy interventions such as proton beam therapy. Many of the contrasting findings may be explained by inconsistent measurement of cognitive outcomes. Of particular significance is that the maximum follow up period in the studies identified by Morrall et al [12] was 5 years. For children treated under 3 years old this yields outcome determination no later than 8 years old in the relatively early part of usually well supported primary school education. Thus there is currently inadequate knowledge of later secondary downstream effects when age matched academic and societal expectations increase. Few studies consider environmental factors such as parental sociodemographic status, which are likely to be important moderators. Furthermore, single centre studies and their associated samples are often insufficient for appropriate data stratification and interpretation. There is evidently a need to include longitudinal, prospective and comprehensive cognitive follow up at specified time points alongside clinical intensive treatment trials.

3. Capturing Cognitive and QoS Outcomes in European Clinical Trials

Given that most childhood tumours are relatively rare, in order to obtain adequate stratified data the challenge is to measure cognitive and psychosocial morbidity in the context of collaborative international trials. A short battery of direct assessments across multiple sites in Germany (WUEP-KD) was successfully applied by Ottensmeier et al. [31] indicating the importance of a cross-battery approach as the fundamental basis of neuropsychological testing in paediatric brain tumour trials. In parallel to this a consensus paper to identify suitable measures for application across European trials, was published in the position paper of Limond et al. (2015) [32] on behalf of the European Society of

Paediatric Oncology (SIOPE) Brain Tumour QoS group. The consensus paper [32] acknowledged and incorporated the short battery of direct assessments identified by Ottensmeier et al but also identified the need to measure additional domains of function considered most crucial for long term childhood brain tumour survivor follow-up, including a common set of cognitive tests, QoS Patient Reported Outcome Measures (PROMs; including proxy parent questionnaires) and endocrine measures.

Kennedy et al. [33] demonstrated the importance of collecting additional QoS outcome data using PROMs, within the SIOPE PNET4 randomised controlled trial for medulloblastoma where 151 of 244 eligible survivors were followed up at a median age of 15.2 years and median 5.8 years from diagnosis. Hyperfractionated radiation therapy (HFRT) was associated with better reported executive function in participants (0.48 SDs) compared with conventional radiotherapy (SFRT), specifically the Inhibition, Shift, Emotional Control, Monitoring, Working Memory, Planning/Organizing scales of the Behaviour Rating Inventory of Executive Function- Parent (BRIEF-P). This is consistent with other published research which has identified executive function deficits in paediatric brain tumour survivors as measured by the BRIEF [34].

Thus PROMs have proven feasible and informative as outcome measures. However, Limond et al [32] stipulate the importance of both direct and indirect measures of outcome. Indeed cognitive assessment is considered the global gold standard in identifying cancer related cognitive impairment [35]. Whilst the PNET4 trial did not include a shared formal protocol for direct assessment, cognitive assessment was undertaken in a cross sectional study of children at mean age (of diagnosis) 9 years in a subset of 137 patients in Germany, Italy, France and Sweden [36]. The Full Scale IQ was reported to be similar in both the HFRT and SFRT groups with both being on average one standard deviation below the normative mean. However, ad hoc analysis indicated that within the HFRT group there was a trend of higher standard scores for verbal IQ ($p=0.02$) and a trend of better processing speed only in the limited sample of those under 8 years old ($p=0.08$). Thus whilst there were a number of limitations to

this study, not least that the test batteries were not consistent between countries, some indicators of differences in outcomes were identified that are important to investigate in future research.

Furthermore, the above study highlighted moderate correlations between the PROMs and direct measures assessing different constructs and weak correlations between the PROMs and direct cognitive measures designed to assess similar constructs. For example, correlations of similar (low) magnitude were found between the BRIEF Metacognition Index and the Wechsler Working Memory Index ($r=.32$) and the HUI health status questionnaire (not expected to measure executive function, $r=0.28$). Conversely, the highest correlations were found between self-reported overall health status and the Wechsler scale indices ($r = 0.35-0.44$) [37]. Additionally, PROMS correlated highly with each other regardless of the domain measured, and principal component analysis identified that direct and indirect measures loaded on two distinct factors. This, therefore, highlights the need to collect longer term follow up data of both direct and indirect measures (which measure distinct aspects of QoS), from a larger group of participants using a consistent battery across participating countries.

4. SIOP-Europe Ependymoma-II Program

The SIOP-Europe Ependymoma-II program (SIOPE EP-II) opened in France and the UK in 2015, followed by Italy, Belgium (2016), Spain, Ireland and Czech Republic (2017), Austria, Switzerland, Finland and Germany (2018) and is currently continuing to open in remaining participating countries. It is a comprehensive international program aiming to improve the accuracy of the primary diagnosis of ependymoma and explore different therapeutic strategies in children, adolescents and young adults accordingly. It incorporates centralised imaging and pathology review, phase II and phase III treatment trials. This program is opened to all patients of participating centres in the enrolled countries across Europe, diagnosed with ependymoma below the age of 22 years. Further to surgery and central review of imaging and pathology, patients are enrolled in one of three different strata (Figure 1) according to

the outcome of the initial surgical resection, and their age or eligibility/suitability to receive radiotherapy.

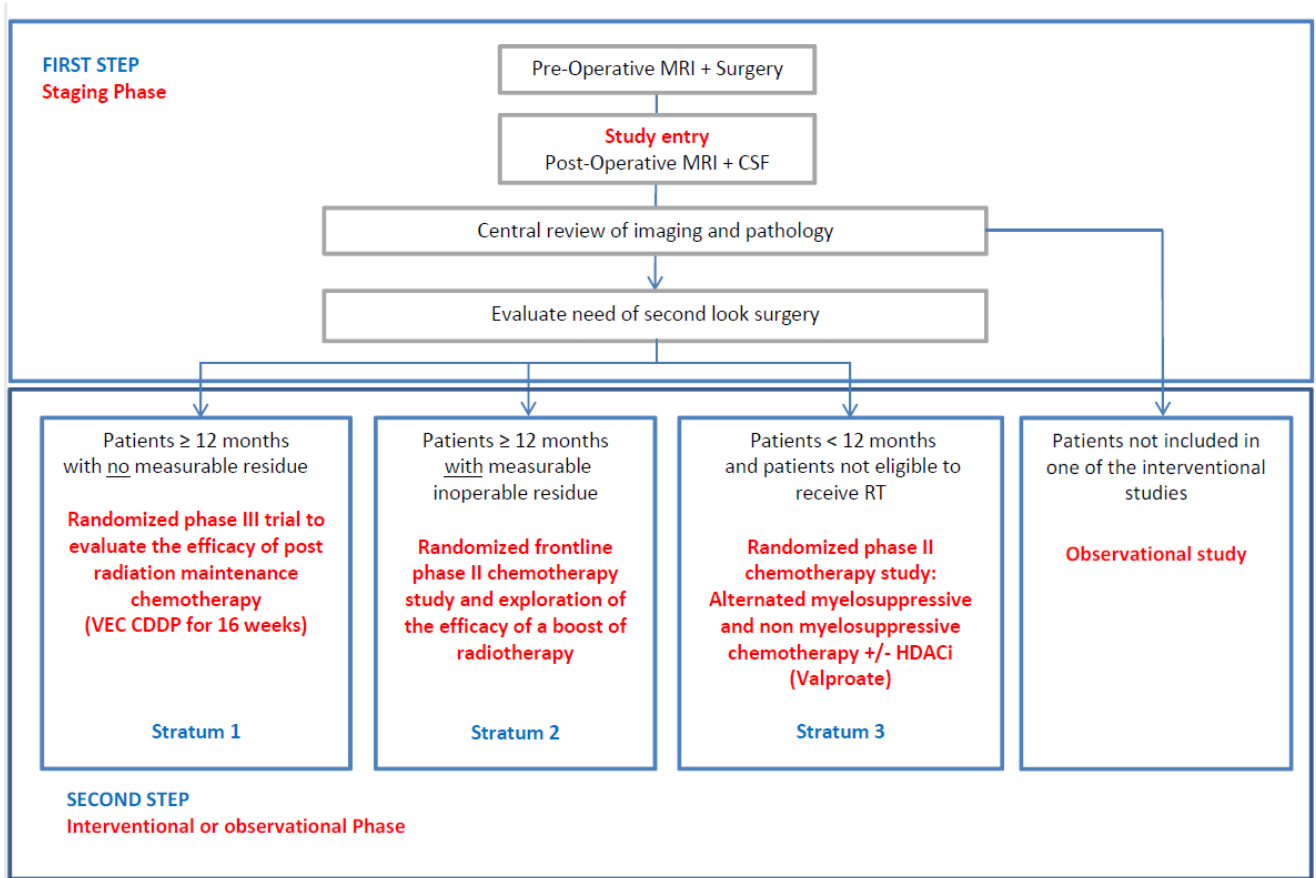


Fig. 1 SIOPE Ependymoma-II Trial Design

In Stratum 1 children who have undergone complete surgical resection are randomised to receive either standard radiotherapy or radiotherapy followed by maintenance chemotherapy. Stratum 2 is opened to participants with centrally confirmed non reoperable residue, who receive a frontline randomised chemotherapy followed by standard radiotherapy and an additional boost, then chemotherapy. Finally, in Stratum 3 infants under 1 year old or those ineligible for radiotherapy are randomised to alternated myelosuppressive chemotherapy either with or without valproic acid.

The aims of the overall program are to improve the clinical outcome of patients with ependymoma by determining whether central review of post-operative MRI can improve the rate of complete surgical

resection and by comparing the efficacy of treatments in each respective stratum as above. There are also a number of further secondary exploratory objectives, including testing the productivity of key molecular events to prospectively evaluate prognostic biomarkers, and evaluation of neuroendocrine morbidity. Endocrine evaluation is to be performed according to individual, clinical needs of the patient, at least once per year until age 18, as serious delayed effects from radiotherapy such as neuroendocrine sequelae and second cancers may occur [38]. Another important secondary objective of the trial is the evaluation of cognitive morbidity and QoS. Indeed SIOPE EP-II is the first large European brain tumour trial protocol to formally include longitudinal evaluation of cognitive morbidity via direct comprehensive cognitive assessment.

5. Developing the Core-Plus Cognitive Test Battery

Ependymoma-specific consensus discussions between QoS representatives of participating European countries were undertaken over a period of approximately 10 years. These included discussions specific to this trial and dialogue integrated within the consensus discussions for the SIOPE BTG QoS group as published in their position paper [32]. Discussions were informed by existing tumour-specific literature, with the aim of establishing a targeted minimum dataset. Negotiating a common battery presented a number of challenges as described below:

5.1 Clinical Context: Capturing cognitive status in an acute hospital context is challenging, particularly at diagnosis, where patients are often unwell and time is constrained by essential ongoing medical investigations. For children in Stratum 1 there can be a limited time window between diagnosis and commencement of radiotherapy, and the opportunity to conduct assessment is further limited for many children who are required to travel to receive proton therapy. Children who are feeling unwell, fatigued and experiencing the significant emotional challenges of becoming hospitalised to undergo repeated aversive medical procedures, are understandably not always able to participate. Some have

visual or motor impairment and a cannula in place which threatens test reliability. Thus, a long battery is unlikely to be feasible in many cases and there is a need for inherent flexibility in any protocol designed for this context.

5.2 Resource Discrepancies: Gathering cognitive outcome data in the context of a clinical interventional trial relies on local clinicians and resources. Discussions revealed that the availability of both test batteries and trained Clinical Psychologists/Neuropsychologists to administer or supervise administration of testing varied widely. In some participating countries cognitive assessment was already part of standard clinical practice. For example, in Germany there is an agreement in place within the Germany Paediatric Brain Tumour Consortium (HIT-Netzwerk) to test all children with brain tumours if possible at year two and five after diagnosis, independent of disease. Three participating countries, UK, Italy and France, successfully applied to national charities to fund neuropsychology provision specifically for this protocol. Other countries had minimal access to psychology or neuropsychology services and only a limited range of standardised tests within immediate access. This translated to discrepancies in feasibility and ambitions with respect to comprehensive cognitive assessment. It became clear that a single test battery would not meet the objectives and constraints of all participating countries, and that there may be a need for a core battery with the option of a more comprehensive extended battery where feasible.

5.3 Multiple Native Languages: Given the potential involvement of 18 European countries, establishing a common test protocol was challenging. Not only did it limit test choice to those available in multiple languages, but a translation lag in gold standard tests such as Wechsler Intelligence Scales deemed it necessary to accept use of multiple editions of these batteries. Translations available naturally influenced preferred test protocols in participating countries. In addition, some domains do not lend themselves to use of the same test across cultures. Where it was not possible to identify tests available in all countries, such as word reading tasks, the protocol allows for tests to be administered

as per national standard, and this will need to be accounted for in the statistical analysis, for example, through conversion to and comparison of z-scores.

6. The Core-Plus Model

Given the above challenges the 'Core-Plus' model (Fig. 2) as introduced in the position paper of Limond et al. (2015) [32] was implemented. This is a two-tier approach to assessment which acknowledges the importance of a minimum dataset for optimal ascertainment but retains flexibility to augment this with optional more comprehensive data collection. It allows essential cognitive domains to be prioritised where test availability and resources are limited, but more comprehensive assessment is conducted using the additional 'Plus' tests where feasible. The tests in Fig. 2 are those applicable to children aged 8 to 16 years, with adaptations specified for younger and older age groups.

Fig. 2 Core Plus Model

WPPSI-III or IV - The Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition [39] or 4th Edition [40]

WISC-IV or V - Wechsler Intelligence Scale Children's 4th Edition [41] or 5th Edition [42]

CMS - Children's Memory Scale [43]

WIAT-II or III - Wechsler Individual Achievement Test 2nd Edition [44] or 3rd Edition [45]

WRAVMA - Wide Range Assessment of Visual Motor Abilities [46]

Beery VMI - Beery-Buktenica Developmental Test of Visual-Motor Integration [47]

D-KEFS - Delis-Kaplan Executive Function System [48]

CPT - Conners' Continuous Performance Test [49]

TEA-Ch - Test of Everyday Attention for Children [50]

CPM - Raven's Coloured Progressive Matrices (CPM) [51]

Vineland II - Vineland Adaptive Behaviour Scales, 2nd Edition [52]

Purdue Pegboard - Purdue Pegboard Test [53]

Due to the challenges establishing an entirely homogenous battery there is some flexibility in the tests to be administered. Countries are asked to complete locally available age appropriate tests of the same domains, or most recently published versions of Wechsler tests, where the recommended tests are not available. For the Plus component of the battery, where discrepancy in availability is greater, each country is asked to specify their alternative but comparable battery and to append this to the protocol. The test or test edition used is specified when data is recorded via a centralised electronic

case report form (eCRF). It is anticipated that the dataset for the Plus component of the battery will be smaller with contributions from countries with greater resource and test availability.

To encourage a consistent minimum dataset and further increase data homogeneity, consensus has recently been agreed for a hierarchical approach to the battery, consistent with the order shown, where those tests considered most crucial are to be administered first.

6.1 Assessment Time Points

All patients entering the interventional phase of the trial, strata 1-3 are eligible for baseline and follow-up cognitive assessment. There are four time points for administration; i) post-surgical baseline which is defined as 7 days post-surgery and within two weeks of commencement of radiotherapy or chemotherapy, ii) 2 year post diagnosis; iii) 5 years post diagnosis; and, iv) 18 years old. This is consistent with SIOPE BTG QoS consensus paper [31]. Early assessment at baseline is completed where feasible to obtain a post-surgical measurement of functioning prior to radiotherapy and chemotherapy intervention. The baseline time window was extended to incorporate two weeks into the commencement of these interventions as completion prior to commencement often proved infeasible. It is recognised that there are confounds at this stage but it was considered important to attempt to capture data, nevertheless. Where baseline assessment is not completed, follow up assessment will continue to be attempted. It is emphasised by country QoS lead personnel that clinical judgement should be exercised by psychologists conducting assessment as to whether assessment is clinically appropriate, particularly where there is considerable ill health and/or distress. The battery is comprised of well-established assessment tools and is not expected to cause distress, but again this is monitored and managed by clinicians delivering assessment.

6.2 Patient Reported Outcome Measures (PROMs)

For children over 5 years old the Core-Plus battery is accompanied by the already established QoS PROMs questionnaires as detailed in Table 2 below. These are the measures employed in the PNET 4

trial [33] and recognised in the SIOPE Brain Tumour QoS group position paper [31]. These are completed by parents for younger children and both the children and their parents for children from 11 years old.

Name of Measure	Patient Completion	Parent Completion
The Health Utilities Index (HUI) [54]	≥ 11 years old	patients ≥ 5 years old
Medical Educational Employment and Social Questionnaire (MEES) [55]	≥ 18 years old	patients between 5 and 17 years old
The Strengths and Difficulties Questionnaire (SDQ) [56]	11 - 17 years old	patients between 5 and 17 years old
EORTC Quality of Life Questionnaire-C30 (EORTC QLQ-C30) [57]	≥ 18 years old	N/A
Pediatric Quality of Life Inventory (PedsQL) [58]	11 - 17 years old	patients between 5 and 17 years old
PedsQL Fatigue Scale (PedsQL Fatigue) [59]	11 - 17 years old	patients between 5 and 17 years old
Multidimensional Fatigue Inventory (MFI) [60]	≥ 18 years old	N/A
The Behavior Rating Inventory of Executive Function (BRIEF) [61]	≥ 18 years old	patients ≥ 5 years old

Table 1: Quality of Survival Questionnaires

6.3 Infants and Young Children

Young children 3 to 5 years old complete subtests of the Wechsler Pre-School and Primary Scales of Intelligence [39] [40] rather than the WISC [41] [42], and for those 42 months old and under, the Bayley Scales of Infant Development- 3rd Edition Social-Emotional and Adaptive Behaviour Questionnaire [62], or another locally available developmental questionnaire, is administered. This provides an alternative indicator of developmental trajectory prior to treatment as a post-surgical baseline measure. It is recognised that many assessment tools for children under 5 years old have poor predictive validity [63] [64] and this can be challenging to administer in the clinical context particularly when children are often unwell and can find it difficult to engage in the assessment

process. The challenge of assessing children under 5 years old is currently being considered by the SIOPE BTG QoS Group and this consensus will soon be submitted for publication.

6.4 Protocol Adherence

Given the large number of participating centres and the detailed protocol, adherence is facilitated by a central co-ordinator in each country. Establishing communication pathways with local centres is crucial. In the UK this process is conducted in partnership with the Cancer Research UK Clinical Trials Unit (CRCTU) who are supporting this trial. In Italy and Germany (for PROMs) centralised co-ordination is made possible via charitable funding. In Germany, direct assessment is initiated via the group of neuropsychologists attached to the HIT-Network. In other countries where the trial has now opened, such as France and the Czech Republic, clinical neuropsychologists have adopted a co-ordinating role within the remit of their clinical posts. The co-ordinator is responsible for prompting centres when assessment should take place, providing support and gathering data. The impact of this co-ordinating post has been demonstrated by the Cancer Research UK charity funded Research Assistant Psychologist commencing 11 months after trial opening. This led to improvement in protocol adherence from 54% of UK patients completing baseline assessment in the first year to 87% in the second year.

It is accepted that testing is not always possible and where testing is not conducted the prohibitive reasons are recorded. This information is utilised to identify how adherence can be improved and will inform future SIOPE trial design. Adherence and obstacles are analysed and reported to the UK Trial Management Group bimonthly, to the European BTG annually, and to the trial sponsor at the Centre Léon Bérard in France, which is responsible for the program as a whole, when requested. This

information is utilised to contribute to ongoing systems and protocol review discussed annually at the SIOPE BTG QoS group international meetings.

6.5 Data Management and Audit

Cognitive test and QoS questionnaire data are collected by designated lead personnel for each country and entered into a specifically designed eCRF, if possible, which takes into account the necessary flexibility in data capture across participating countries. The eCRF facilitates recording of different test versions or locally available tests alongside any visual, hearing or motor impairment. Data are scored and entered to the eCRF centrally in each country to minimise error. Monitoring of data includes audit of data transfer, test scoring and eCRF input. Quality control checks are recommended on 10% of test data. Where corrections are required there is a full audit trail.

6.6 Statistical Analysis

Data will be analysed by the trial statistician in collaboration with the lead neuropsychologist. Specific analysis will be guided by the quantity and quality of the data. The Core-Plus battery has been designed to capture performance on specific domains considered important for this population. Thus analysis will reflect this and will not rely entirely on composites such as Full-Scale IQ which do not take into account the potential subtest performance variability and the impact of confounding factors, such as sensory impairment, on particular subtests.

A detailed Statistical Analysis Plan will be composed by the statistician, in consultation with the research team, prior to analysis. Patient test scores over time will be analysed using mixed-effects

modelling allowing for adjustment for post-surgical baseline measurements, important covariates such as age at diagnosis and other likely prognostic factors such as socioeconomic status, parental education and peri-operative complications such as posterior fossa syndrome and hydrocephalus. This analysis will allow for an assessment of any changes in trend over time for these scores for each randomised treatment arm within stratum to ascertain the impact of treatment on cognitive ability. Each domain will be individually analysed using this methodology. Descriptive statistics will be further provided for these measures.

6.7 Dissemination

Findings will be disseminated via publication in an international journal and presented at international conferences regardless of the outcomes. It is planned that both outcomes and learning from the process of conducting comprehensive cognitive assessment in a multinational trial will be published. Test data will be archived at the country lead institutions in line with relevant national legal and statutory requirements.

7. Preliminary Findings of Protocol Implementation

The early stages of the SIOP EP-II trial are providing an opportunity to apply the Core-Plus battery in the baseline phase, where patients are receiving the initial diagnosis and entering the trial. This was expected to be the most challenging phase due to the clinical and time constraints already described, and the flexibility of the battery is proving useful. The Core battery has been used as a minimum dataset under time and resource constraints, whereas the Core-Plus has been implemented in centres with appropriate resources and where clinical circumstances allow. Monitoring of adherence rates and obstacles, as described above, has revealed the importance of clear and timely communication with local centres and consequently proactive management of patients to enhance cognitive protocol

adherence. In July 2017 when the trial had been open 27 months in France, 17 months in the UK and 18 months in Italy, 63% of patients had been assessed at post-surgical baseline and this has remained relatively consistent though improvement is hoped for as test availability is improved in some countries. Some participants had only achieved partial completion of the Core components, due to delays in test availability, largely for the visuomotor tests.

Other obstacles to adherence have included local staffing resources, poor local understanding of the protocol, unavailability of tests and patients being too unwell. Some of these obstacles have been addressed and are an inherent component of the early stages of a large trial; others are unavoidable and to be both expected and accepted. Assessment of children 3 to 4 years of age has proved more challenging than anticipated, due to test discrepancies on WPPSI editions and some reluctance of children at this age to engage with assessment around the time of diagnosis. A protocol amendment to include a developmental questionnaire option for children 3 to 4 years old is under consideration.

As test batteries have developed it has been necessary to review the Core-Plus battery to include new editions of tests such as the WISC V. The flexibility already inherent due to a lack of perfect homogeneity across Europe facilitates this. There will no doubt be a requirement for further modification in the future to reflect progress in measurement tools and lessons learned from this study. Consensus discussions have also included potential measurement of broader factors such as psychological distress, parenting stress, participation and self-efficacy. There was insufficient consensus and availability of measures across Europe for inclusion at this stage, but these discussions will no doubt continue.

It is likely that the Core-Plus model will be compatible with other international test protocols. In particular it is noted that there are distinct similarities between this test battery and the ALTE07C1 battery employed in the US Children's Oncology Group study of the neuropsychological, Social, Emotional, and Behavioural Outcomes in Children with Cancer [65]. This creates future possibilities for shared larger datasets and global collaboration. Learning from this trial is also being applied to the design of future European brain tumour trials. The Core-Plus concept can be applied in other trials even where specific test batteries differ, due to the flexibility our model affords in mandating a feasible minimum dataset whilst not excluding more comprehensive assessment. For these reasons we propose that the Core-Plus model offers a solution for cognitive follow up in other childhood disease groups associated with cognitive sequelae.

8. Conclusion

European consensus has been reached for an internationally accepted test battery for follow-up of childhood ependymoma survivors. The Core-Plus battery mandates a minimum dataset but retains flexibility for more comprehensive assessment where feasible. It is therefore suitable for application across multiple national and international clinical trials in a wide range of disease groups. It will allow more robust evaluation of the long-term outcomes for children considered to be at both low and high risk of cognitive morbidity and to compare these findings. These data will be combined with QoS questionnaires and endocrine follow up findings to provide comprehensive overview of quality of survival. Furthermore, the Core Plus battery shares tests in common with other internationally mandated batteries making wider global collaboration and shared datasets a future possibility.

Findings from initial protocol implementation have illustrated the importance of working collaboratively and seeking to understand clinicians' perspectives across Europe in order to create achievable test protocols and thus facilitate optimal data collection. There is a need to consider the potential conflict between cognitive assessment for clinical purposes and for research data collection and how protocols are designed to meet both purposes where required.

Early data suggest good adherence to the protocol but this will continue to be monitored. The role of a funded central co-ordinator in all participating countries is proving to be crucial to success. It is expected that there will be further learning throughout the progress of this trial which will be disseminated in due course to inform design of future collaborative international trials.

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